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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,448	WEISS ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-39* is/are pending in the application.

4a) Of the above claim(s) *14-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Rejection of May 6, 2005 on November 10, 2005 and on March 2, 2006. Claims 1-8, 11 are amended. Claim 13 is cancelled. Claims 14-38 are withdrawn. Claim 39 is new.

Claims 1-12, 39 are under consideration.

Change of Inventorship

AD 5/12/06

Applicant's petition under 37 CFR 1.48(a) to add Anthony J. Khim as an inventor is granted. In view of the petition filed November 10, 2005, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding the inventor, Anthony J. Khim.

Withdrawn Rejections

35 U.S.C. § 112, 2nd parag.

Applicant's amendments and arguments, see page 14 of Applicant's response, filed November 10, 2005 and on March 2, 2006, with respect to the rejection of claims 1-13 have been fully considered and are persuasive. The rejection of claims 1-13 has been withdrawn.

35 U.S.C. 102(a)

Applicant's arguments, see pages 15-16 of Applicant's response, filed November 10, 2005, with respect to the rejections of claims 1-8 have been fully considered and are persuasive. Applicant has changed the inventorship of the Application such that Kihm et al. no longer qualifies as prior art under 102(a). The rejection of claims 1-8 has been withdrawn.

35 U.S.C. 103(a)

Applicant's arguments, see pages 15-16 of Applicant's response, filed November 10, 2005, with respect to the rejections of claims 9-13 have been fully considered and are persuasive. Applicant has changed the inventorship of the Application such that Kihm et al. no longer qualifies as prior art under 102(a). The rejection of claims 9-13 has been withdrawn.

Maintained and New Rejections/Objections

Information Disclosure Statement

As indicated in the Office Action of May 6, 2005, page 6, the information disclosure statement filed August 30, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed.

Applicant indicates that the publications by Schaeffer and dos Santos appear to have been lost by the Patent Office and are submitting in a second paper, a new PTO

1449 and IDS requesting that these references be considered by the Examiner (Applicant's response, page 10, 3rd parag.). While Applicant provides this response, it is noted that neither a new 1449 or publications have been received by the Office.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-12, 39 are newly rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available at http://uspto.gov/web.menu.utility.pdf, the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

The instant claims are drawn to a transgenic mouse, wherein both alleles of Alpha Hemoglobin Stabilizing Protein (AHSP) have been disrupted via targeted insertion of a transgene, wherein said mouse does not express a functional mouse AHSP and erythrocytes obtained from said mouse exhibit one or more characteristics selected from the group consisting of abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin, to a transgenic mouse, wherein one allele of AHSP has been disrupted via targeted insertion of a transgene, wherein said mouse exhibits an elevated reticulocyte count, and to a method of screening for agents that affect AHSP activity, using the claimed mice. The specification identifies the following uses for the claimed mice: 1) the use of the mice to understand the role AHSP plays in disease processes (specification, page 27, 1st parag. under "II. Transgenic Animals with an Altered AHSP Genotype"); 2) the use of the mice to establish a non-human model for disease involving the under

expression or non-expression of AHSP (specification, page 27, 2nd parag. under "II. Transgenic Animals with an Altered AHSP Genotype"); and 3) the use of the mice to identify or evaluate diagnostically or therapeutically effective agents.

In regards to asserted utility 1), as identified above, the stated utility of the mice for evaluating the role of the AHSP gene or gene product or for defining disease pathways associated with the AHSP gene or gene product does not constitute a real world utility and therefore is not a substantial utility, but rather represents further research on the product to identify or reasonably confirm a real world utility. As stated in the Guidelines set forth above, research that involves studying the properties of the claimed product itself does not constitute a substantial utility. Further, such an asserted utility constitutes a general, rather than a specific utility, as all knockout mice can be used to study the effects of the loss of function of the gene that is disrupted. Therefore, asserted utility 1) does not meet the standard for a specific and substantial utility.

In regards to asserted utility 2), as identified above, while the specification teaches that the homozygous AHSP knockout mice exhibit reticulocyte counts that were elevated about 3 fold and that erythrocytes obtained from homozygous AHSP knockout mice exhibit an abnormal speculated morphology (specification, page 48, parag. under "Results/Discussion"). In the case of the heterozygous AHSP knockout mice, the mice exhibited reticulocyte counts that were mildly elevated (specification, page 49, 1st parag.), nothing in the specification teaches that these phenotypes are associated with a disease or can in fact be used as a model for any particular disease. Thus, in the absence of any specific teachings as to diseases associated with AHSP disruption in

mice, the asserted utility of the mice as disease model is neither specific nor substantial as it would require further research to identify a disease associated with the AHSP gene, if any exist, and to correlate any observed phenotype or characteristics of the mouse with the characteristics of that disease.

In regards to asserted utility 3), as identified above, since the specification fails to teach any disease associated with AHSP, the use of the mice to identify an agent that modulates a phenotype associated with AHSP function or to identify diagnostic or therapeutic agents for AHSP associated diseases is neither specific nor substantial as no disease associated with AHSP has been identified. As such, the asserted utility does not constitute a real world use of the claimed mice as it would require further research to identify a phenotype or disease associated with the AHSP gene, if any exist, and to correlate any potential phenotype found in the mouse with a characteristic of a AHSP associated disease.

Thus, in view of the discussion above, the skilled artisan would not find any of the asserted utilities of the transgenic mouse, cells derived from the mouse, targeting construct, or embryonic stem cells encompassed by the claims to be specific and substantial, or well-established.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 39 are rejected in modified form under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record, May 6, 2005.

The specification indicates that the focus of the claimed invention is that the claimed transgenic mouse comprises a disruption in its endogenous AHSP in its genome, wherein said mouse does not express functional AHSP, and wherein erythrocytes obtained from said mouse exhibit one or more characteristics selected from the group consisting of abnormal speculated morphology, reduced lifespan, increased production of reactive oxygen species (ROS), and precipitated hemoglobin. In the case of mice comprising a heterozygous disruption of AHSP, the mice exhibit an elevated reticulocyte count. While the specification provides this teaching, the specification does not teach whether these mice are model for any AHSP-associate disease or disorder. As such, the use of the claimed mice is not readily apparent.

The claims broadly encompass homozygous and heterozygous mice comprising a disruption in its AHSP gene. However, at the time of filing, the art teaches that the phenotypes of knockout mice were unpredictable. In addition, the art did not consider the correlation between any observed mouse phenotypes and human disease phenotypes as predictable. Doetschmann et al. teaches that "[o]ne often hears the comment that genetically engineered mice, especially knockout mice, are not useful because they frequently do not yield the expected phenotype, or they don't seem to

have any phenotype (Doetschmann,1999, Lab. Animal Sci., 49: 137-143, see page 137, column 1, paragraph 1)." Doetschmann provides numerous examples of instances in which genes considered well-characterized *in vitro* have produced unexpected phenotypes or indiscernible or no phenotypes in transgenic or knockout mice. Moens et al. further teaches that different mutations in the same gene can lead to unexpected differences in the phenotype observed. Moens et al. shows that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embyronic stem cells, one leaky and one null (Moens et al.,1993, Development, 119: 485-499). Further, the art demonstrates the unpredictability of making a mouse model for human disease by disrupting the murine gene. Jacks et al. teaches that although retinoblastoma (Rb) gene mutations in humans are associated with retinal tumors, Rb gene knockout mice had tumors in the pituitary gland rather than the retinas (Jacks et al., 1992, Nature, 359: 295-300). Likewise, whereas HPRT deficiency in humans is associated with Lesch-Nyhan syndrome, a severe neurological disorder, HPRT-deficient mice are phenotypically normal (Kuehn et al.,1987, Nature, 326, 295-298 and Jaenisch, 1988, Science, 240, 1468-1474). Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of transgenic or knockout mouse even when the activity of the gene has been extensively studied *in vitro*, and further establishes the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans.

In addition to the phenotypes of knockout mice being unpredictable, the art teaches that while the promise of gene targeting had been to reveal the *in vivo* function

of a gene of interest, the functional relevance of gene targeting has been questioned because the mutation might lead to an avalanche of compensatory processes (up- or downregulation of gene products) and resulting secondary phenotypical changes. Thus, a null mutant organism might not only lack the produce of a single gene, but might also possess a number of developmental, physiological, or even behavioral process that have been altered to compensate for the effect of the null mutation (Gerlai, 1996, Trends Neurosci, 19: 177-181, page 177, 1st col., 1st parag.). Gerlai teaches an example wherein background genotype can confound the exhibited phenotypes. Targeted disruption of a gene of interest, α, might lead to changes in expression of alleles b and B for gene β. A regulatory change in gene β might lead to different phenotypic changes, depending on which allele (b or B) is present in the organism with the null mutation in gene α. The upshot of this problem is that due to this polymorphism in the genetic background, one cannot conclude for certain that a phenotypic change exhibited in a null-mutant mouse resulted from the null mutation or to the genetic background (Gerlai, page 177, 1st col., under "Polymorphism in the genetic background might make the results of gene-targeting studies difficult to interpret"). As this applies to the instant invention, while the intent of the invention is to determine whether the claimed mouse is a model for a condition in the human, the art indicates that whatever phenotype is exhibited in the mouse cannot reasonably be predicted to be biologically related to the gene of interest. Rather, further characterization would need to be carried out to determine the relationship between gene and phenotype.

For these reasons, the claimed invention is not enabled.

Response to Arguments

Applicant's arguments, see pages 11-14 of Applicant's response, filed November 10, 2005 and on March 2, 2006, with respect to the rejections of claims 1-12 have been fully considered and are persuasive in part. The withdrawal and maintenance of the rejections are as follows.

Claim 13 has been cancelled. Rejections pertaining to claim 13 have been withdrawn.

Applicant has amended the claim to address the issue that it is unclear whether the mice in claim 2 were fertile or unfertile (Applicant's response, page 12). The rejection regarding this issue is withdrawn.

Applicant has amended the claims to address the issue of "null mutation" in claims 3-8 (Applicant's response, page 12). The claims have been amended to replace the phrase "null mutation" with "transgene". The rejection regarding this issue is withdrawn.

Applicant provides a response to the method for screening for therapeutic agents which affect AHSP activity in knockout AHSP mice and indicates that the specification provides a number of different AHSP activities to assess in connection with the screening method encompassed by claim 9. The Examiner does not find the argument persuasive because as indicated on page 18 of the Office Action, the mice used in the screen have no AHSP protein. As such, nothing in the specification or the art indicates

how to screen for agents that affect AHSP activity when the mice do not express AHSP. The rejection regarding this issue is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 39 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 39 recites the limitation "said agent" in claim 9. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH